Remarks

Claims 19-21, 27-41 and 43 are pending. Claims 21, 39 and 43 have been amended. Claims 1-18, 22-27, 30 and 42 have been cancelled without prejudice. Applicants reserve the right to pursue the deleted subject matter in one or more divisional, continuation, or continuation-in-part applications.

Claims 21, 39 and 43 have been amended to delete reference to SEQ ID NO:1. No new matter has been added.

Rejection Under §103

I. U.S.C. § 103 Rejection of Claims 19-20, 28, 29, 31-34, 37 and 38

Claims 19-20, 28-29, 31-34 and 37-38 have been rejected under 35 U.S.C. §103(a) as being obvious over International Publication WO 02/059321 (hereafter "De Francesco") in view of US Patent No. 6,297,003 (hereafter "Rice I") and International Publication WO 01/89364 (hereafter "Rice II") and further in view of US Patent No. 6,063,562 (hereafter "Melnick") and US Publication No. 2004/0018529 (hereafter "Li"). Applicants respectfully disagree.

A. Claims not requiring inclusion of a portion of a clinical isolate

De Francesco teaches HCV replicons with adaptive mutations to enhance replicon activity. The replicon sequences disclosed are that of HCV con-1, a consensus HCV sequence. De Francesco does disclose that other naturally occurring HCV 3' UTRs can be used. Although the 3' UTR from HCV-1a is not specifically mentioned, it is a naturally occurring UTR as the

Examiner points out. However, broad, generic disclosures are inadequate to establish obviousness as to a species. *See Ashland Oil*, 776 F.2d at 296-97, 227 U.S.P.Q. at 666-67; *In re Jones*, 958 F.2d 347, 349-50, 21 U.S.P.Q. 2d 1941, 1943 (Fed. Cir. 1992) (disclosure of a genus in a prior art reference does not in itself render a species of that genus obvious).

The Examiner contends that he has cited De Francesco not for its broad disclosure but rather to indicate that any UTR can be used. Rice I was cited as specifically disclosing a number of HCV-1a 3' UTR sequences. However, a closer look at the disclosure of Rice I reveals that it does not remedy the deficiency of De Francesco. While Rice I does disclose specific HCV 3'UTR sequences, they are not restricted to HCV-1a sequences, nor or HCV-1a singled out as better than the sequences of other strains. Of the 17 specific 3' UTR sequences recited (*i.e.*, SEQ ID NOS:1-4, 20-24, 28-31 and 33-36), only 5 are from HCV-1a (*i.e.*, SEQ ID NOS:20-24). The remaining sequences are derived from HCV-1b, HCV-3, HCV-4 and HCV-4a. (see col. 11, lines 20-57; col. 17, lines 55-62). Applicants believe that this disclosure is analogous to the disclosure of De Francesco where the 3' UTR of HCV-1a was not pointed to as being more advantageous than any other 3' UTR. As such, Applicants contend that there is no specific suggestion to use HCV-1a 3'UTR even when combining De Francesco and Rice I.

Additionally, the Examiner had stated that substitutions of HCV-1a 3'UTR into the replicons of De Francesco would have been obvious because "those of ordinary skill in the art would have been motivated to make such substitutions because the art indicates that the 3' UTRs of Rice are functional equivalents for the sequences provided in De Francesco" (see page 6, lines 2-4 of the Office Action mailed July 9, 2007). However, the Examiner had provided none of the art that describes the 3' UTRs of HCV con-1 and HCV-1a as equivalent. In response, the

Examiner has clarified his position by stating that "the teachings of De Francesco [that naturally occurring HCV 3' UTRs and functional equivalents thereof can be used in replicons] indicate that the HCV 3'UTRs may act as functional equivalents of each other, and therefore provide adequate basis to render the use of any known HCV 3' UTR obvious" (see page 4, first full paragraph in the Office Action mailed November 30, 2007).

Applicants respectfully disagree. De Francesco states that two types of 3'UTRs can be used - - namely naturally occurring HCV 3'UTRs and functional equivalents of naturally occurring HCV 3'UTRs (see page 10, lines 23-30 of De Francisco). This statement does *not* imply that all naturally occurring HCV 3'UTRs are functional equivalents of each other as the Examiner has characterized. Accordingly, the Examiner must still cite art that describes the 3' UTRs of HCV con-1 and HCV-1a as equivalent. The rejection of a claim based on the Examiner's opinion, without additional evidence, is impermissible. *In re Zeidler*, 682 F.2d 961, 967 (CCPA 1982).

B. Claims requiring inclusion of a portion of a clinical isolate

The Examiner admits that neither De Francesco nor Rice I teach or suggest using HCV regions isolated from clinical isolates in the disclosed replicons. The Examiner cites to De Francesco as teaching that HCV replicons can contain 3'UTR sequences from different HCV subtypes or strains. The Examiner combines this teaching with the teaching from Rice II that HCV replicons can have portions (including non-structural polypeptides) from different HCV strains or subtypes. However, Rice II still does not teach or suggest using portions of HCV from clinical isolates. The Examiner contends that the teaching or suggestion of using portions of

HCV clinical isolates in an HCV replicon can be inferred from Rice II. Applicants respectfully disagree.

Rice II discloses that replicons can be used to screen for anti-viral compounds and should have "wild type" sequences. The Examiner interprets this to suggest use of clinical isolate sequences. However, throughout Rice II, the term wild type is consistently used to refer to a starting sequence *before* mutation. Any examples of altered sequences of HCV after replication in cell culture are referred to as adaptive *mutations* or *variants* (see, *e.g.*, page 62, lines 18-30 of Rice II). The Examiner is taking that one statement in Rice II with respect to wild type sequences and is viewing it through the prism of the Applicants' disclosure to interpret it to mean clinical samples. Without the improper of use of hindsight, one of skill in the art would not have taken that statement in Rice II to mean clinical sample isolate sequences.

Even assuming *en arguendo* that the reference to "wild type" in Rice II does mean a clinical isolate sequence, Applicants still fail to see how such a statement would be interpreted by one skilled in the art as pertaining to the cited statements concerning sequences from different HCV subtypes or strains to arrive at the claimed chimeric replicons.

The Examiner also cites Melnick and Li as teaching the use of clinical isolate sequences. Melnick is directed to methods of predicting the identity of HIV protease mutants that emerge in response to drug treatment. Applicants note that throughout Melnick, clinical isolate sequences are referred to as "mutant" rather than "wild type" as in Rice II. The passage cited by the Examiner as having relevance to the instant application (*i.e.*, column 11) is directed to the use of their disclosed methods to evaluate the efficacy of a drug against various proteases, some of which can be mutant forms from clinical isolates.

Li is directed to methods of cloning genes encoding proteins involved in proteolytic cleavages and methods of finding protease inhibitors. The passage cited by the Examiner as having relevance to the instant application (*i.e.*, paragraph 9) is in the Background section of Li where identification of protease inhibitors are said to be important because a number of viruses use proteases in their life cycle. Li proposes that their disclosed methods can be adapted to screen clinical isolates of HIV for drug resistance.

Applicants pointed out that neither Melnick nor Li are directed to HCV or the use of any methods using a replicon. The mere mention of using clinical isolates of other viruses for other purposes would not lead one skilled in the art to interpret the teachings of De Francesco, Rice I or Rice II in the way the Examiner alleged.

In response, the Examiner contends that Melnick and Li were cited as providing a general motivation in the art to develop drugs against pathogens which develop resistance to known drugs during the course of infection (see page 5, lines 10-14 of the Office Action mailed November 30, 2008). Merely identifying a problem is not tantamount to solving that problem. Applicants point out that just because drugs are desired against clinical isolates of a pathogen or that resistance to drugs in target pathogenic populations change over time, it does not follow that others skilled in the art would solve the problem in the same manner as does the present invention. The Examiner has used Applicants' novel solution as frame to piece together individual parts of separate prior art references to recreate the claimed invention. This is prohibited. *W.L. Gore & Assocs. Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552, 220 U.S.P.Q. 303, 312 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) and *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1 U.S.P.Q.2d 1593 (Fed. Cir. 1987), *cert. denied*, 481 U.S. 1052 (1987).

Furthermore, none of the art cited by the Examiner actually made a chimeric replicon with a portion coming from clinical isolate HCV. Applicants believe that they are the first to make a replicon containing portions from both lab propagated replicons and clinical isolate HCV nucleic acids that can infect patients. It is unexpected that a functional replicon could be obtained using nucleic acids from two such disparate sources.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection under §103.

II. U.S.C. § 103 Rejection of Claims 35-36

Claims 35 and 36 have been rejected under 35 U.S.C. §103(a) as being anticipated by De Francesco in view of Rice I, Rice II, Melnick and Li in view of US Patent 5,783,669 (hereafter "Hawkins"). Applicants respectfully disagree.

Dependent claims 35 and 36 are directed to the chimeric HCV replicons of claim 20 that further have non-naturally occurring restriction sites in the replicon. As discussed *supra*, Applicants contend that De Francesco, Rice I, Rice II, Melnick and Li do not render claim 20 obvious. If the base claim from which a claim depends is not made obvious by the cited references, then the dependant claim is not obvious over those same references as well.

Hawkins is cited to show that modifications to nucleic acid sequences could be made without affecting the encoded amino acid sequence. Applicants contend that this does nothing to remedy the deficiencies of De Francesco, Rice I, Rice II, Melnick and Li.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection under §103.

Double Patenting

Claims 19-20, 28, 29, 31-34, 37, and 38 have been provisionally rejected for nonstatutory obviousness-type double patenting as being unpatentable over claims 9 and 10 of co-pending application Serial No. 10/543,633 (hereafter "'633 application"). Applicants respectfully disagree with the Examiner's characterization of the subject matter of the claims as being patentably indistinct.

In an Amendment Under 37C.F.R. § 1.111 filed on December 21, 2007 in the '633 application, claims 9 and 10 were amended such that only SEQ ID NO: 1 or the nucleic acid that encodes SEQ ID NO:1 (*i.e.*, SEQ ID NO:3) are claimed. SEQ ID NO: 1 is a HCV NS3-NS4A-NS4B-NS5A-NS5B polyprotein based on HCV-BK. SEQ ID NO: 3 is an HCV replicon that was constructed by replacing the NS3 through 3'-UTR sequence of the HCV-con1 replicon with the corresponding region from HCV-BK. (see paragraphs 24 and 138 of US Patent Publication 2006/0228697 corresponding to the '633 application) Thus, the claimed replicon has a 3'UTR region from BK which is HCV-1b. All of the currently pending claims in the instant specification require that the replicons have a 3'UTR from HCV-1a. Thus, the cited claims of the '633 application and the currently pending claims are *not* indistinct.

Additionally, claims 20, 31-34 and 37 require that a portion of the replicon be from a clinical isolate. There is no such modification in SEQ ID NOS: 1 or 3 in the '633 application.

In view of the foregoing, Applicants respectfully request withdrawal of the double patenting rejection.

Claim Objections

Claims 21 and 39-43 are objected to as containing unelected subject material. In response to the second Restriction Requirement issued in connection with this application, Applicants provisionally elect, with traverse, the replicon of SEQ ID NO:2 over SEQ ID NO:1 as the species to be examined. Applicants have amended the claims to exclude reference to SEQ ID NO:1.

In view of the foregoing, Applicants respectfully request withdrawal of the objections to the claims.

Conclusion

It is believed that the claims now pending are in condition for allowance. Early and favorable action by the Examiner is earnestly requested.

Authorization

The Commissioner is hereby authorized to charge to deposit account 13-2755 $510.00 to pay the fee for a Notice of Appeal. Additionally, the Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to deposit account 13-2755.

Respectfully submitted,

Dated: February 29, 2008 By: _____

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